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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|

| EXAMINER | |
|---|---|
| ART UNIT | PAPER NUMBER |

**DATE MAILED:**

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/485,943 | Applicant(s) Friedman et al. |
|---|---|---|
| | Examiner J. Railey | Group Art Unit 1805 |

☒ Responsive to communication(s) filed on *18 Jun 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *54-131* is/are pending in the application.

Of the above, claim(s) *54-123 and 125-131* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *124* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *12*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

The Examiner and Art Unit location for your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1805, Examiner Railey.

Applicant's election of Group VII, claim 124 in Paper No. 11, received 18 June 1997 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 54-123 and 125-131 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 11.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 124 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a gene encoding the mouse OB polypeptide as shown in SEQ ID NOs 1 or 2 for reducing the body weight of *ob/ob* mice or normal mice, does not reasonably provide enablement for using other "allelic variants or analogs, including fragments, thereof having the same biological activity," or enable treating animals other than mice with the mouse OB protein disclosed. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 124 depends upon claim 54, which is drawn to an OB polypeptide "having about 145 to about 167 amino acids, capable of modulating body weight in an animal, or allelic variants or analogs, including fragments, thereof having the same biological activity." [The OB protein is now known as the "leptin" protein.] Given the disclosure of the mouse gene encoding the mouse OB polypeptide in SEQ ID NO: 1, as well as the deduced corresponding amino acid sequence in SEQ ID NO:2, the skilled artisan could make and use the mouse gene to express mouse OB polypeptide. Because of codon degeneracy, applicant could also argue that any DNA sequence encoding the OB protein as shown in SEQ ID NO: 2 could be constructed and inserted into an expression vector. The skilled artisan could easily make other OB genes encoding the same amino acid sequence given therein. The specification teaches that when the purified mouse OB protein is administered to either genetically obese mice (*ob/ob*) or to normal weight mice, there is a resulting drop in body weight. Although the specification does not show any examples of administration of nucleic acid encoding this protein for expression of functional mouse OB polypeptide *in vivo*, the specification does envision the creation of mammalian expression vectors for delivery of this gene to animals. See pages 57, 74 and 83 of the specification as filed. The vector may be used to modify cells *ex vivo* followed by administration of these modified cells, or the vector may be delivered *in vivo* for expression of the OB protein. Others in the art later

confirmed applicant's proposed use of disclosed adenoviral or retroviral vectors to deliver the OB gene to mice. See Muzzin et al. [Proc. Natl. Acad. Sci. USA **93:**14804-14808 (1996)], Fletcher et al. [Experimental Hematology **24(9)**:1055, abstract 172 (1996)] and Fletcher et al. [Blood **86(10 Suppl. 1)**:241A, abstract 951 (1995)].

There are two issues regarding enablement of the scope of claim 124. The first is in regard to the specific amino acid sequence of the OB polypeptide claimed. The second is in regard to the animal shown to have actual weight loss by the increased levels of OB protein *in vivo*. Other than the specific mouse OB protein taught in SEQ ID NO: 2 which is shown to reduce the body weight of mice, no other OB genes, variants, alleles or fragments thereof are taught in the specification to reduce the body weight of any other mammals. In particular, as the specification discloses the specific sequence of the gene encoding the human OB polypeptide, it is not demonstrated that humans, either of normal weight or obese, can actually have a modification of body weight by increased levels of the OB polypeptide *in vivo*.

Regarding the first issue, the specification fails to identify other allelic variants, analogs or fragments thereof which would have the same "biological activity". Which amino acids can be altered and still give a protein which modulates body weight like the native sequence described in SEQ ID NO:2? There are potentially 20 different amino acids which may be substituted at any number of positions in the protein. Such claims also embrace an unspecified number of amino acid insertions or deletions. How and where can the gene be fragmented and still encode

a protein having activities commensurate with the native protein? Determination of such fragments would constitute undue experimentation. The specification fails to provide sufficient guidance as to what constitutes a variant having the properties as claimed. Such claims are inadequately supported by the disclosure and applicant has failed to provide enablement for the invention as broadly claimed. The skilled artisan is given no guidance whatsoever as to what would constitute such allelic variants. Hence the experimentation would inherently be considered undue to practice the invention as claimed. See *In re Deuel* 34 USPQ2d 1210 (CAFC 1995); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d 1016 (CAFC 1991); *Colbert v. Lofdahl* 21 USPQ2d 1068 (Bd. Pat. Ap. and Inter. 1991); and *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997).

Regarding the second issue, although applicants have taught the gene sequence encoding the human OB polypeptide, there is no teaching that humans can be treated with this gene and cause a resulting increase in OB production and a modification (i.e. reduction) of body weight. As shown by Muzzin et al., administration of a vector containing the leptin protein will cause a "total correction of the obese phenotype of the *ob/ob* mice." See page 14807, second column, last full paragraph. However, increasing the levels of leptin protein may not necessarily correct the body weight of all obese mice. See Campfield et al. [Science **269:**546-549 (1995)] at page 548, third column, first full paragraph. Genetically obese *db/db* mice do not respond to increased levels of leptin. Clearly, weight loss in individual obese mice may be dependent upon

the nature of the genetic defect, with *ob/ob* mice susceptible to the effects of increased levels of leptin protein. Obesity in humans may result from environmental as well as genetic factors. See Sorensen et al. [Metabolism **44(9 Suppl 3):**4-6 (1995)]. Reduction of body weight in obese humans may not be as simple and straightforward as increasing leptin levels as seen in genetically defined mouse models. See Ferrell [Human Biology **65(6):**967-975 (1993)] at page 973, first full paragraph and Lindpaintner [The New England Journal of Medicine **332(10):**679-680 (1995)], at page 680, second column, last paragraph. Finally, the teachings of Maffei et al. [Diabetes **45:**679-682 (1996)] states that defects in the OB coding region "are not a common cause of obesity in humans." See page 681, second column under DISCUSSION. It is unclear whether most individuals who are obese are so due to defects in the regulatory regions of the OB gene or for some other unrelated reason. The specification fails to demonstrate that increased expression of the OB polypeptide in humans would result in modification of body weight in any individual. Particularly in obese individuals, the specification fails to identify the population of individuals which would benefit from the administration of the leptin gene to modify body weight as claimed. Given the lack of guidance of the specification on how to affect body weight changes in humans, the uncertainty in the state of the art as to the complex causes of obesity in humans, the unpredictability of gene therapeutics in general in the art and the lack of any current art recognized genetic alterations of body weight in humans, it would require undue experimentation to practice the invention for its scope.

Claim 124 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 124 depends depend upon non-elected claim 54. Applicant should amend claim 124 to include all the limitations of the base claim. Claim 54 states that the OB polypeptide is "about 145 to about 167 amino acids." This is a vague description of the polypeptide having the capability of modulating body weight; it sets forth no specific polypeptide sequence. How much is "about" 145 or 167 amino acids? The term "about" is not defined in the specification. Also claim 54 is confusing as constructed. It appears that the "allelic variants or analogs" is referring to the animal and not the polypeptide. Finally, the term "biological activity" is not defined. Does applicant mean that the biological activity is the ability to modulate body weight. All proteins have biological activity in that they can be used as antigens.

Regarding claim 124, the method involves "administering a nucleic acid". The composition of this nucleic acid is unclear. The specification discusses including the OB gene in vectors for delivery to cells *ex vivo* or directly *in vivo*. Other than administration of vectors comprising the OB gene, it is unclear what is the composition of this nucleic acid as claimed for administering to the mammal.

The specification at page 155, line 16 is objected to as lacking the specific SEQ ID NO. Clarification is required.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Art Unit 1805 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number for Art Unit 1805 is (703) 308-4242 or 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. F. Railey, whose telephone number is (703) 308-0281. The examiner can normally be reached on Monday-Thursday, and alternate Fridays, from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax phone number for informal transmissions to the examiner is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

23 September 1997

**JOHNNY F. RAILEY II, PH.D.**
**PATENT EXAMINER**
**GROUP 1800**